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ScienceDirect
The Veterinary Journal 177 (2008) 26–35
The Veterinary Journal
www.elsevier.com/locate/tvjl

Review

The feline acute phase reaction

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Accepted 7 June 2007

Abstract

The acute phase reaction (APR) is a response to potentially pathogenic stimuli. It begins with the release of interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-α from inflammatory cells. These cytokines induce fever, leucocytosis and release of serum acute phase proteins (APPs). In this review, the characteristics of the feline APR are described. In cats with inflammatory conditions, fever is a common finding, with leucocytosis due to the release of cells from the marginal pool, followed by activation of myelopoiesis. Because excitement frequently causes leucocytosis in cats, a diagnosis of inflammation should therefore be supported by additional findings such as the presence of toxic neutrophils. The major APPs are serum amyloid A and α_1-acid glycoprotein (AGP), which both increase a few hours after the inflammatory stimulus and remain elevated for as long as the inflammation persists. AGP plays an important role in the diagnosis of feline infectious peritonitis (FIP) and may also be useful also in studies of FIP pathogenesis.

Keywords: Feline; Acute phase reaction; Fever; Leucocytosis; Acute phase proteins

Introduction

The term acute phase reaction (APR) describes a series of pathophysiological events that occur in animals exposed to potentially pathogenic stimuli. The pathogenesis of the APR begins within inflammatory sites, where cells involved in the innate immune response (i.e., macrophages and, to a lesser extent, neutrophils) produce and release pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-α (Bochsler and Slauson, 2002). A similar pattern of cytokine production is however also involved in the host response to some types of tumours that are thus able to evoke a typical APR even in the absence of exogenous inflammatory stimuli. IL-6, for example, can be produced by a number of different cell types (such as keratinocytes, endothelial cells and fibroblasts) under the influence of circulating IL-1 and TNF-α. This cytokine activation and release leads to high levels of IL-1, IL-6 and TNF-α in the blood (Moshage, 1997; Gabay and Kushner, 1999).

These cytokines influence organs involved in homeostasis, such as the central nervous system (CNS), the autonomic nervous system (ANS) and the adrenal gland, ultimately to establish a rapid and intense protective/reactive response. In the CNS, cytokines induce a cascade of events which potentiate the cytokine-induced response, so favouring the appearance of the three hallmarks of the APR, namely fever, leucocytosis and changes in the concentration of serum acute phase proteins (APPs). In addition, the stimulation of the CNS results in activation of a variety of responses, mostly mediated by the hypothalamo–pituitary–adrenal and hypothalamo–pituitary–gonadal axes, inducing behavioural changes including lethargy, anorexia, adipsia and a disinterest in social and sexual activities (Karrow, 2006; Owen-Ashley et al., 2006).

Experimental studies have demonstrated that both lipopolysaccharide (LPS) and cytokines released by LPS-stimulated inflammatory cells activate the two components of the ANS, namely the sympathetic and the parasympathetic

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doi:10.1016/j.tvjl.2007.06.005

systems to release catecholamines and acetylcholine, respectively (Tracey, 2002). These two molecules interact with nicotinic and adrenergic receptors, which are expressed in various cell types, including hypothalamic and immune-inflammatory cells. The activation of the ANS can thus depress the release of cytokines by inflammatory cells and influence hypothalamic responses, thus modulating the APR (Karrow, 2006). These multi-directional communication pathways, which are summarised in Fig. 1, have been recently explored in humans and in laboratory animals. No data about possible peculiarities of the feline neuroendocrine response are available, but anorexia, depression and behavioural changes are frequently seen in cats during inflammation.

In this review, the mechanisms responsible for fever, leucocytosis and APP production will be briefly described; attention will then be focused on the diagnostic utility of APPs in feline medicine. Although techniques to investigate cytokine gene expression have already been established in cats (Rottman et al., 1995; Kipar et al., 2001; Gelain et al., 2006), the majority of studies on cytokine production by feline cells have examined the response to specific virus infections (Gunn-Moore et al., 1998; Linenberger and Deng, 1999; Dean et al., 2003; Foley et al., 2003; Kiss et al., 2004; Dean et al., 2006; Kipar et al., 2006) and little is known about the molecular pathogenesis of feline APR. What information is available, however, indicates that the production of cytokines by feline monocytes decreases from youth to middle age then increases in the elderly cat, thus explaining the frequent appearance of inflammatory conditions in younger and older animals (Kipar et al., 2005). It would also seem that pro-inflammatory cytokines are produced in cats in response to LPS treatment (Otto and Rawlings, 1995) as has been demonstrated in other species.

Fever

Most cytokines are unable to pass the blood-brain barrier, although in cats it has been demonstrated that circulating IL-6, rather than IL-6 produced in the brain, induces the febrile response (Akarsu et al., 1998). The action of pro-inflammatory cytokines on the CNS is, therefore, mainly modulated by the local production of intermediate molecules such as prostaglandins (PGs), which, in turn, activate hypothalamic centres responsible for thermoregulation, or by the cytokine-induced release of leptin from adipocytes. Leptin can freely cross the blood-brain barrier and directly stimulate hypothalamic thermoregulatory centres.

In vitro studies have demonstrated that feline cerebral microvessels do not respond to endotoxin or to IL-1 by producing PGE_2 (Bishai et al., 1987). Nevertheless, prostanoids do increase in the brain of febrile cats (Sirko et al., 1989) and inhibitors of cyclooxygenase 2 (COX-2), one of the enzymes responsible for PGE_2 formation, are efficacious in attenuating LPS-induced fever (McCann et al., 2005). This suggests that in cats PGE_2 may be involved in the pathophysiological mechanisms responsible for fever (Sirko et al., 1989).

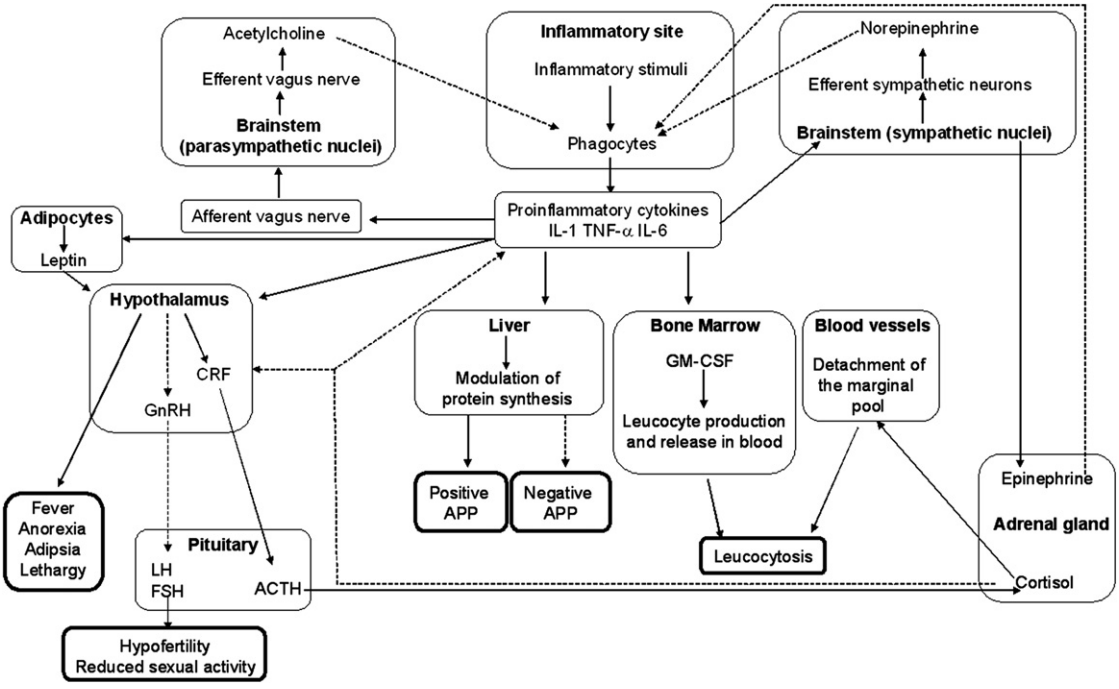

Fig. 1. Summary of the mechanisms responsible for the clinical signs and laboratory findings in the acute phase reaction (circled by the thick line). Solid lines indicate stimulatory effects; dashed lines indicate inhibitory effects. IL-1, interleukin-1; TNF-α, tumour necrosis factor α; IL-6, interleukin-6; CRF, corticotrophin releasing factor; GnRH, gonadotropin releasing hormone; LH, luteinising hormone; FSH, follicle stimulating hormone; ACTH, adrenocorticotropic hormone; APP, acute phase protein.

Fever is a powerful diagnostic indicator of inflammation and a very common finding in cats with infections or inflammatory reactions, although it can be caused by other stimuli such as tumours or degenerative conditions (Wess et al., 2003; Weiss, 2005), or after anaesthesia and surgery, even in the absence of septic complications (Posner et al., 2007). As a consequence, it is difficult in many cases to identify the reason for the increased body temperature and the only possible final diagnosis in many hyperthermic cats is 'fever of unknown origin' or 'antibiotic-responsive fever' (Lappin, 2002). In contrast, in the case of localised inflammation, fever may not be present, as reported by Sergeeff et al. (2004), who found only three febrile cats out of 14 with hepatic abscesses.

Leucocytosis

In addition to causing fever, cytokines at the hypothalamic level are responsible for the production of corticotropin releasing factor (CRF), which, in turn, activates the hypophysis to release adrenocorticotrophic hormone (ACTH). The adrenal glands respond to ACTH by producing cortisol. Cortisol might modulate the inflammatory response and exert a local anti-inflammatory effect, but at a systemic level it is involved in determining both leucocytosis and APP production. Cortisol has multiple effects on inflammatory/immune cells, mainly mediated by modulation of the expression of cytokines, adhesion molecules and molecules involved in leukocyte maturation, differentiation and trafficking, and is responsible for the first wave of neutrophils (polymorphonuclear leucocytes, or PMNs) that appears in the blood just after an inflammatory stimulus.

APR-induced leucocytosis is biphasic. The increase in cortisol induces a rapid increase in circulating leucocytes since, in association with IL-1, cortisol causes a decreased adhesiveness to the endothelium of mature neutrophils belonging to the so called marginal pool, which become detached from the endothelium and enter the blood (Smith, 2000). This is particularly important in cats, since the ratio between circulating and marginal pool leucocytes is about 1:3, whereas in other species it is nearer 1:1 (Cowell and Decker, 2000; Smith, 2000). The cells belonging to the marginal pool cannot, however, sustain the peripheral demand of phagocytes for a long time, since neutrophils are short-lived cells, and most will leave the circulation by diapedesis to move into inflamed tissues where they are attracted by exogenous or endogenous chemoattractants.

A second and more long-lasting wave of neutrophils follows the activation of bone marrow myelopoiesis, again induced by IL-1 and TNF-α released into the blood at the start of an inflammatory event. As they stimulate the CNS and the neuroendocrine axis, they also stimulate bone marrow competent cells to produce haematopoietic cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), which, in turn, activate myeloid precursors to replicate and differentiate into bands, and then segmented neutrophils.

This process takes some hours or days. In healthy individuals, the maturation of feline neutrophils takes about 6 days, but it is longer in calves and humans (7 and 14 days, respectively). Once released into the bloodstream, the half-life of feline neutrophils ranges from 5.5 to 7.6 h. They then move into the tissues where they die by apoptosis within 4 days (Smith, 2000). During inflammation, maturation time is accelerated by cytokines and steroids, and within 12–24 h (approximately when PMNs released from the marginal pool begin to die and disappear from the circulation) newly formed PMNs appear in the circulation. Cytokines accelerate the delivery of PMNs to the inflamed tissues, thereby reducing the half-life of circulating PMNs; moreover, apoptosis is delayed by glucocorticoids, TNF and IFN-γ, thus increasing the life of PMNs in tissues. It is therefore important to note that the dynamics of neutrophils during inflammation differ from that found in normal, healthy individuals.

Theoretically at least, within a few minutes of an inflammatory stimulus the leucocyte count in feline blood may triple and remain high for a long period. Nevertheless, the actual leucocyte count depends on the equilibrium between the rate of PMN production and tissue demand. It is possible that in the case of exaggerated tissue demand, leucocytosis can be mild or characterised by the presence of circulating immature forms (the so called 'left shift'). Other possible sources of 'hyperacute' leucocytosis are common in cats, especially as a consequence of excitement, fear or stress (Cowell and Decker, 2000). Although these latter stimuli might be easily differentiated from APR-induced leucocytosis (since they are characterised by increases in both lymphocytes and neutrophils), it is not rare to have 'mixed' leucocytotic patterns (with elevations of both neutrophils and lymphocytes) in cats with inflammation. A rapid increase in leucocytes is not, therefore, absolutely specific for inflammation.

Segev et al. (2006) have shown that only about 50% of cats with subacute or chronic inflammation actually had increased number of neutrophils and the degree of neutrophilia was usually higher when inflammation was localised (e.g. in abscesses, pyometra etc.), than in generalised infections, where neutropenia frequently occurs (Cowell and Decker, 2000). Accordingly, a lack of leucocytosis does not necessarily exclude the presence of inflammation. Indeed, the most prevalent finding in cats with inflammation seems to be the presence of toxic neutrophils (Segev et al., 2006).

The three main toxic changes in neutrophils are cytoplasmic basophilia (suggesting a higher rate of enzyme production), vacuolation (probably due to activation of lytic enzymes) or granulation, such as Dohle bodies, which are aggregates of endoplasmic reticulum frequently found in feline blood and can suggest the presence of inflammation when associated with leucocytosis or left shift (Smith, 2000).

The acute phase proteins

The third hallmark of the APR is the modulation of protein synthesis by hepatocytes (Baumann and Gauldie, 1994; Bochsler and Slauson, 2002). The concentrations in blood of the acute phase proteins, or APPs, can vary by >25% after an inflammatory stimulus. Some will increase (positive APPs), whilst the concentration of others decreases (negative APPs).

The mechanism responsible for altered protein synthesis, involves cytokines released from inflammatory sites (IL-1, IL-6 and TNF-α) and also endogenous glucocorticoids. The cytokines act in a synergistic manner: TNF-α mobilises peripheral amino acids by activating a proteolytic process in muscles, thus increasing the molecules available for the liver to synthesise new proteins. IL-1 is key in modulating hepatic protein synthesis since it has an inhibitory effect on the synthesis of negative APPs and, by contrast, a stimulatory activity on the synthesis of positive APPs. This latter effect depends also on a permissive action of glucocorticoids. Finally, IL-6 facilitates the release of APPs in blood (Ceciliani et al., 2002). This complex pattern of induction is defined as 'type I response' but some APPs are induced mainly by IL-6, according to a 'type II response' (Petersen et al., 2004).

In species other than the cat, albumin is the most important negative APP. The decreased synthesis of albumin allows a huge amount of amino acids to become available for use in the synthesis of positive APPs. Transferrin, apolipoprotein A1, retinol binding protein, cortisol binding protein and transthyretin, are other negative APPs. No data about the possible role of albumin as a negative acute phase protein in cats are available, and although it has been reported to decrease in many feline inflammatory conditions (Thomas, 2000; Ottenjann et al., 2006) it has not been proven whether this decrease depends on extravasation of albumin from vessels to inflamed tissues or to true decreased hepatic production. Similarly, no information on the role in cats of the other negative APPs is so far available. However, most of these proteins transport vitamins, hormones and/or oligoelements, and their decrease allows the amount of biologically active 'free' molecules to increase. It is thus reasonable to presume that they work as negative APPs also in cats.

The group of positive APPs includes a vast number of proteins. The most well known are C-reactive protein (CRP), complement fractions (C3 and C4), α_1-acid glycoprotein (AGP), LPS binding protein (LBP), haptoglobin (Hp), ceruloplasmin (Cp), serum amyloid A (SAA), α-globulins with antiprotease activity (e.g. α_1-antitrypsin) (Ceron et al., 2005). The group of positive APPs tends to increase continuously with the inclusion of newly discovered molecules, such as, for example, hepcidin, a protein involved in regulating iron metabolism during inflammation (Nemeth et al., 2003; Fry et al., 2004), or of molecules that are involved in processes different from inflammation but that are characterised by the typical 'APP behaviour' (e.g. showing an increase of >25% during inflammation). This is the case with antithrombin III, which may work as an APP in cats (Brazzell and Borjesson, 2007).

It has been proposed that the term 'acute phase protein' should be replaced with 'acute phase reactant'. The two terms are generally considered to be synonymous, but the latter would also include non-protein molecules such as total serum syalic acid, which increases during inflammation (Gopaul and Crook, 2006), or proteins involved in APRs but traditionally considered separately from APPs, such as the same APR-inducing cytokines or hormones ghrelin, leptin, and gonadotropins, the concentrations of which vary during APR (Maruna et al., 2005; Owen-Ashley et al., 2006). In the present review, only the 'classical' APPs will be discussed.

In most cases, the function of positive APPs has not yet been fully understood. Generally the main function of these proteins is to contribute to body defences during inflammation by modulating the efficiency of the immune system (CRP, C3 and C4, AGP, LBP), by transporting molecules to prevent their potential loss (Hp, Cp) or by protecting tissues from excessive damage generated by inflammatory mediators (SAA, α_1-antitrypsin). Most of these APPs, however, have more than one function (Petersen et al., 2004): Cp, for example, can act as transporter of copper and as antioxidant (Giurgea et al., 2005), CRP binds bacterial peptides but also modulates the response of some inflammatory/immune cells (Zhong et al., 1998), and Hp binds free haemoglobin and is also able to influence neutrophil functions (Rossbacher et al., 1999). The function of the most important feline APPs will be discussed below. More extensive information about the function of other positive APPs can be found in recent reviews by Murata et al. (2004) and Ceron et al. (2005).

Diagnostic utility of APPs

Once inflammatory stimuli induce APP production and release, the concentration of positive APPs begins to increase within a few hours, peaks in 24–48 h, and remains elevated as long as the inflammatory stimulus persists. For this reason they represent the ideal tool for the early identification of inflammation and for monitoring the outcome of inflammatory processes.

The magnitude of the APP increase, however, is variable. Compared to baseline values, which are often negligible, some APPs increase by less than 2-fold, others 3- to 10-fold or even 10- to 1000-fold (Table 1). Based on these magnitudes, APPs have been classified as 'minor', 'moderate' or 'major' (Bochsler and Slauson, 2002; Murata et al., 2004; Petersen et al., 2004; Ceron et al., 2005). The magnitude of the increase varies in different species and each has its own major and minor APPs (Ceron et al., 2005). Some authors prefer to use the terms 'minor' or 'major' on the basis of which protein more frequently increases in a given species, independent of the magnitude of the increase (Gruys and Toussaint, 2001). These two different ways of

Table 1
Summary of physico-chemical characteristics of the most important positive acute phase proteins in different animal species

	EF	MW (kDa)	g/dL	Group	Major	Minor
Haptoglobin (Hp)	α_2	100–400	1–2.6	II	$B_{(III)}$, $S_{(III)}$, $M_{(III)}$	$H_{(II)}$,$C_{(II)}$,$F_{(I/II)}$,$R_{(II)}$
Complement fraction C3	$\alpha_1-\beta$	185	0.8–1.4	I	None	$All_{(I/II)}$
Complement fraction C4	α_1	206	0.2–0.4	I	None	$All_{(I/II)}$
Ceruloplasmin (Cp)	α_2	51	0.2–0.6	I	None	H,C,F,B
Fibrinogen	$\beta-\gamma$	341	2.0–4.5	II	None	$H_{(II)}$,$E_{(II)}$,$B_{(I)}$,$S_{(I)}$,$M_{(II)}$,$R_{(II)}$
α_1-Acid glycoprotein (AGP)	α_1	41	0.5–1.4	II	$F_{(II)}$,$R_{(III)}$	$H_{(II)}$,$C_{(II)}$,$B_{(II)}$,$M_{(II)}$
C reactive protein (CRP)	α_2	106	<0.01	II	$H_{(III)}$,$C_{(III)}$,$E_{(II)}$,$S_{(II)}$,$M_{(II)}$,$R_{(II)}$	$F_{(II)}$,$B_{(I)}$
Serum amyloid A (SAA)	α_2	14	0.01	III	$All_{(III)}$	None
Serum amyloid P (SAP)	–	–	–	III	$R_{(I/III)}$	None
α_2-Macroglobulin (2MG)	α_2	–	–	III	None	$B_{(II)}$,$R_{(III)}$
Pig major acute phase protein (Pig-MAP)	α_2	115	–	III	$S_{(III)}$	$B_{(II)}$, $R_{(II)}$

EF, electrophoretic migration; MW, molecular weight; g/dL, physiological concentration in serum; Group: proteins are listed according to the usual increase during the acute phase reaction (APR): I = increase up to 100%, II = increase up to 10×, III = increase >10× during APR.
Major or Minor = species in which each APP is considered major or minor based on the frequency of increase during APR and on the magnitude of elevation (see I, II and III above); B = bovine; C = canine; E = equine; F = feline; H = human; M = mouse; S = swine; R = rat.
Modified from Gruys and Toussaint (2001) and Petersen et al. (2004).

classifying positive APPs partly overlap since in many cases the protein that most frequently increases in a given species also shows a higher magnitude of increases compared to other species. The important concept is that each animal species has its own 'major' APP that must be considered the marker of choice for diagnostic purposes (see Table 1). In cats, the positive APPs which play a major role in the diagnostic approach are SAA and AGP (Petersen et al., 2004; Ceron et al., 2005).

From a diagnostic point of view, the rapid increase in major positive APPs represents a great advantage for early diagnosis of inflammatory conditions. Unfortunately, APP increases are poorly specific, since they increase in the presence of inflammation independent of the agent responsible (with the sole exception of AGP for the diagnosis of feline infectious peritonitis). This is a disadvantage, but the increase in APPs indicates that 'something' is happening in the body and should lead the clinician to investigate the site, type and severity of the inflammation (by means of clinical findings, diagnostic imaging and a complete clinico-pathological approach), and to identify the pathogen responsible (using specific serological, bacteriological or molecular approaches).

During the follow-up, monitoring APP levels is important in clinical decision making. Once the inflammatory stimuli have been eliminated, APP concentration decreases earlier than other indicators of disease (which can remain elevated until pathogen-induced lesions have been repaired), but will remain elevated if the pathogen persists in the body (in spite of possible normalisation of physical or clinico-pathological parameters induced by supportive therapies). In this case, treatment should be changed or modified until a true response has been achieved.

How to measure APPs

Most positive APPs migrate as α- or β-globulins (Gruys and Toussaint, 2001). A simple zonal serum protein electrophoresis can thus provide generic information about the presence of inflammatory conditions, which usually result in increased α.-and/or β-globulins (Thomas, 2000). This finding, however, is extremely vague, since on the one hand other proteins with α-or β-motility exist (e.g. lipoproteins, transport proteins) but on the other hand it does not reveal which protein is actually responsible for the increases.

Several methods are available for measuring specific APPs. These include the colorimetric method proposed by Eckersall et al. (1999) to measure Hp based on its ability to bind haemoglobin, and many immunological methods such as radioimmunoassay (RIA), ELISA, radial immunodiffusion tests or nephelometry (Gruys et al., 2005). The interpretation of results from haemolytic, icteric and lipaemic samples should be interpreted with caution, due to the possible influence of these interfering substances on analytical results (Ceron et al., 2005). Most methods are time-consuming, however, and relatively expensive, so limiting the wide-scale use of APPs in routine practice. Recently, immunoturbidimetric tests for measuring feline APPs have been validated (Bence et al., 2005; Hansen et al., 2006) and should probably reduce the cost per test, thus allowing greater use of APPs measurement.

A possible future challenge for veterinarians would be the development of high throughput techniques, such as protein microarray methodology, which would allow simultaneous measurements of thousands of samples per batch, as has already proposed for species other than the cat (Toussaint et al., 2004; Gruys et al., 2005). In addition, techniques able to detect qualitative or structural changes to the APPs, such as two-dimensional gel electrophoresis, high performance liquid chromatography (HPLC), Western blotting and lectin staining, are available (Ceciliani et al., 2004; Miller et al., 2004; Cunningham et al., 2004). These techniques, however, are currently used only for research purposes, due both to their cost and to the need for specialised equipment and trained personnel.

Feline APPs

Contrary to reports in other species, data regarding APP levels in cats are scarce and mostly focused on general aspects of feline APP biology, such as the demonstration of the lack of age-related changes in APP concentration in feline serum (Campbell et al., 2004), basic and comparative information about APP gene and protein structures (Mominoki et al., 1995; Yoshida et al., 1997; Ohno et al, 1999; van Rossum et al., 2004) or methodological aspects of measurement of feline APPs (Katnik et al., 1998; Kajikawa et al., 1996; Sasaki et al., 2001). Most feline APP studies have been focused on AGP, SAA and, to a lesser extent, Hp - the three proteins which have been shown to work as major APPs in the cat. Pathophysiological conditions in which increased AGP, SAA or Hp concentrations have been recorded are listed in Table 2. All of these proteins, with the exception of CRP, were higher in hospitalised cats compared to healthy controls, and all showed a 2–4 fold increase 24 h after surgery, independent of the presence of possible post-surgical complications, or after experimentally induced inflammation (Kajikawa et al., 1999).

Apart from sporadic studies, where Hp was included among other indicators of inflammation in specific diseases (Gouffaux et al., 1975), the first report on feline Hp was by Harvey and Gaskin (1978), who described increases in cats with several experimentally induced pathological conditions. However, Hp did not change in cats with haemolytic anaemia due to haemoplasmas, in spite of the role of Hp in binding free haemoglobin after haemolytic crises. Increased Hp in anaemic cats with inflammatory conditions were reported recently by Ottenjann et al. (2006). In feline infectious peritonitis (FIP), a particularly high Hp value was demonstrated in affected cats (Gouffaux et al., 1975; Duthie et al., 1997) in which Hp increased very early, then slightly decreased, only to increase again a couple of weeks after experimental induction of the disease (Stoddart et al., 1988).

Serum amyloid A (SAA) is a major feline APP as in many other species. SAA works as scavenger of potentially dangerous oxidised cholesterol but also has immunomodulatory activities (He et al., 2006). Feline SAA concentrations increase early during inflammation (Kajikawa et al., 1999), especially in FIP (Giordano et al., 2004), but the magnitude of the SAA increase in cats (about 10–50×) is lower than in other species (>100× in humans) (Kajikawa et al., 1999; Ceron et al., 2005). SAA also increases during renal failure, neoplasms, liver disorders and diabetes (Sasaki et al., 2003). Its specificity as a marker of inflammatory conditions is thus limited, although the magnitude of increase is usually higher in cats with inflammation compared with cats with non-inflammatory disorders (Sasaki et al., 2003).

Monitoring circulating SAA or sequencing SAA might be useful in Somali, Abyssinian or Oriental cats, which can develop systemic amyloidosis where elevated serum

Table 2
Summary of feline pathological or pathophysiological conditions in which increases in APPs have been reported

Disease	Increased APP	Reference
Anemia of inflammatory diseases (localised purulent infections)	Hp, AGP	Ottenjann et al. (2006)
Diabetes	SAA	Sasaki et al. (2003)
Experimental inflammation	Hp, SAA, AGP	Harvey and Gaskin (1978), Kajikawa et al. (1999)
Feline coronavirus (FCoV) infection (non-symptomatic)	AGP*	Ceciliani et al. (2004), Giordano et al. (2004), Paltrinieri et al. (2006), Paltrinieri et al. (2007a)
Feline calicivirus infection	AGP	TerWee et al. (1997)
Feline chlamydiosis	AGP	TerWee et al. (1998)
Feline leukaemia virus (FeLV)	AGP	Duthie et al. (1997)
Feline infectious peritonitis	Hp, SAA, AGP*	Harvey and Gaskin (1978), Bence et al. (2005), Duthie et al. (1997), Giordano et al. (2004), Kaijkawa et al. (1999), Paltrinieri et al. (2007a), Stoddart et al. (1988)
Feline immunodeficiency virus (FIV)	AGP	Duthie et al. (1997)
Hospitalisation	Hp, SAA, AGP	Kajikawa et al. (1999)
Infectious diseases (miscellaneous)	Hp, AGP, SAA	Harvey and Gaskin (1978), Sasaki et al. (2003), Hansen et al. (2006), Paltrinieri et al. (2007a)
Injury	SAA	Sasaki et al. (2003)
Lymphoma	AGP	Correa et al. (2001)
Oriental and Abyssinian cats (healthy and with amyloidosis)	SAA*	DiBartola et al. (1989)
Renal failure	SAA	Sasaki et al. (2003)
Splenectomy	Hp	Harvey and Gaskin (1978)
Surgery	Hp, SAA, AGP	Kajikawa et al. (1999), Sasaki et al. (2003)
Tumours	AGP	Selting et al. (2000), Sasaki et al. (2003)
Urinary tract diseases	SAA	Sasaki et al. (2003)

* Structural changes also reported.

levels of SAA (DiBartola et al., 1989) and amyloidogenic SAA sequences (Niewold et al., 1999) are found. In these cats, the SAA produced during non specific mild inflammation and extravasated from blood to tissues cannot be completely proteolysed and undergoes a partial proteolysis which generates SAA fibrils with β-sheet conformation and consequent accumulation as amyloid in the tissues.

The majority of studies on feline APPs have been focused on AGP, and especially on its serum or tissue concentrations in cats with FIP. AGP, previously known as orosomucoid, belongs to the lipocalin family, a group of extracellular binding proteins specific for hydrophobic molecules, and specifically to the immunocalin subfamily, which includes proteins with immunomodulating properties (Lögdberg and Wester, 2000). Human AGP is characterised by low molecular weight (41–43 kDa), high solubility, very low pI (2.8–3.8) and high percentage of carbohydrates (45%). Its glycosylation pattern is very variable (12–20 glycoforms) depending on the physiological or pathological conditions, such as pregnancy, inflammation or cancer (Biou et al., 1991; Kim and Varki, 1997).

The function of AGP has not been completely defined. However, an immunomodulatory and anti-inflammatory role has been suggested as it can down-regulate neutrophil responsiveness, stimulate IL-1R antagonist secretion by macrophages, inhibit platelet aggregation and lymphocyte proliferation and modulate the production of anti-inflammatory cytokines by peripheral blood leucocytes (Hochepied et al., 2003). These activities are correlated to the carbohydrate moiety (Shiyan and Bovin, 1997). In particular, the rate of sialylation has been proven to be protective in inflammation and in human immunodeficiency virus (HIV) infection (Rabehi et al., 1995).

In the cat, AGP increases with spontaneous or experimentally induced inflammation (Kajikawa et al., 1999). It can also increase in cats with neoplasms (Selting et al., 2000), particularly lymphoma (Correa et al., 2001) although the intensity of AGP increases seems not to have a prognostic role, as has been found in dogs (Tecles et al., 2005).

Most studies on feline AGP have focused on infectious diseases (TerWee et al., 1997,1998), with a particular emphasis on FIP. FIP is a lethal disease caused by feline coronavirus (FCoV) that is difficult to diagnose by conventional approaches (Addie et al., 2004). AGP increases in FIP have been identified for many years during experimental infections (Stoddart et al., 1988). In tissues harvested from cats with FIP, AGP seems to be associated with viral antigen and is present in large amounts (Paltrinieri et al., 2004), together with a low-molecular weight AGP-like molecule which is also expressed on inflammatory cells (Paltrinieri et al., 2003). Studies of spontaneous infections have confirmed that although high serum AGP concentration can be found in cats with feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) infection, AGP increases are so evident as to be diagnostic for the disease (Duthie et al., 1997). Similarly, high AGP levels within effusions can be used to confirm a clinical suspicion of wet FIP (Bence et al., 2005). Nevertheless, it has been demonstrated that non-symptomatic shedders of FCoV also have cyclic fluctuations of serum AGP, probably due to continuous re-infection (Giordano et al., 2004). Based on this finding, AGP levels should be interpreted with caution in cats living in catteries where the disease is endemic.

When AGP levels from FCoV-infected, clinically healthy cats, from cats with inflammatory and non-inflammatory disorders and from cats with FIP are compared, it has been demonstrated that, in the case anamnestic, clinical and clinico-pathological changes, indicate a high pre-test probability of FIP, also moderate serum AGP levels can be diagnostic for FIP (Paltrinieri et al., 2007a). Apart from these quantitative changes, the hypothesis that different AGP glycoforms might play a role in determining resistance or susceptibility to infectious diseases (Rabehi et al., 1995) has stimulated several researchers to examine the structural characteristics of feline AGP in cats with FIP.

Feline AGP has wide polymorphisms that might account for different glycoforms (Yoshida et al., 1997) and it has been shown that AGP purified from the serum of cats with FIP is hyposyalilated (Ceciliani et al., 2004; Cunningham et al., 2004). Interestingly, the fluctuation in AGP levels in clinically healthy, FCoV-positive cats (Giordano et al., 2004) occurred a few days before the occurrence of episodes of FIP in a cattery, when the percentage of FCoV-shedders and median antibody titres also increased in those cats that remained healthy (Paltrinieri et al., 2007b). In contrast, after FIP outbreaks, antibody titres, percentage of shedders and AGP levels of cats that did not develop the disease decreased, but increased the degree of α(2–3) syalilation of serum AGP (Paltrinieri et al., 2006). These findings raise interesting questions about possible FCoV–AGP interactions that might play a pathogenic role in FIP or indeed a protective role against FCoV infection, depending on the glycoforms, and also on the possible roles of α(2–3) and α(2–6) syalic acid as binding molecules of coronaviruses and other pathogenic viruses (Schwegmann-Wessels and Herrler, 2006).

Conclusions

The APR is a powerful tool for combating potentially dangerous pathogens and experimental data suggest that APPs play a major role in feline inflammation. Unfortunately, the molecular events that lead to this reaction have not yet been fully investigated, and this is particularly the case in the cat. Diagnostically, however, the three main hallmarks of APR (fever, leucocytosis and changes in serum APPs) are all seen in cats with inflammation and can therefore be very useful in routine procedures for the early diagnosis of inflammatory conditions, and to monitor progress.

APPs are reliable biomarkers and can be used both in diagnostic approaches and for research purposes.

Specifically, Hp, SAA and, especially, AGP should be included in laboratory panels to diagnose inflammation in cats. Their use should be facilitated in future by the availability of newer and cheaper analytical techniques that will allow larger scale measurement of these proteins, and by the availability of more sophisticated molecular methods to investigate the structural characteristics of APPs. Of particular value may be feline AGP which, as with its human counterpart, seems to play an important but still undefined role in determining resistance or susceptibility to infectious disease.

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